

Impact of remdesivir for the treatment of COVID-19 during the first wave in Spain

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Abstract

Background: Spain was one of the most affected countries during the first wave of COVID-19, having the highest mortality rate in Europe. The aim of this retrospective study is to estimate the impact that remdesivir -the first drug for COVID-19 approved in EU- would have had in the first wave.

Methods: This study estimated the impact on the Spanish National Health System (SNHS) capacity (bed occupancy), and the number of deaths that could have been prevented, based on two scenarios: a real-life scenario (without remdesivir), and an alternative scenario (with remdesivir). It considered the clinical results of the ACTT-1 trial in hospitalized patients with COVID-19 and pneumonia, who required supplemental oxygen. The occupancy rates in general wards and ICUs were estimated in both scenarios.

Results: Remdesivir would have avoided the admission of 2,587 patients (43.75%) in the ICUs. It would have also increased the SNHS capacity in 5,656 general wards beds and 1,700 ICU beds, showing an increase in the number of beds available of 17.53% (95% CI: 3.98% - 24.42%), and 23.98% (95% CI: 21.33% - 28.22%), respectively, at the peak of the occupancy rates. Furthermore, remdesivir would have avoided 7,639 deaths due to COVID-19, which implies a 27.51% reduction (95% CI: 14.25% - 34.07%).

Conclusions: Remdesivir would have relieved the pressure of the SNHS, and would have reduced the death toll, providing a better strategy for the management of COVID-19 during the first wave.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), originated in Wuhan (China), causes a respiratory illness designated as coronavirus disease 2019 (COVID-19), which has become a global pandemic. In the beginning of December 2020, the World Health Organisation (WHO) registered almost 70 million cases of COVID-19 and more than 1.5 million deaths worldwide [1]. Spain is one of the European countries more severely affected by the ongoing pandemic [2], with more than 1.7 million cases of COVID-19 and close to 50,000 deaths at the end of 2020 [1].

The COVID-19 pandemic also implied an increasing number of transmissions and hospitalizations, resulting in a significant burden for the Spanish National Health System (SNHS) [3]. In the worst times of the pandemic, hospitals were forced to expand the number of beds available for COVID-19 patients in improvised ward areas [4]. In addition, the management of the increasing number of cases and the preventive measures delayed the diagnosis, treatment, monitoring, and non-emergency surgeries of other patients [5–7]. Furthermore, due to the concerns about the risk of COVID-19 infection, some patients avoided going to healthcare centres and hospitals, increasing the morbidity and mortality of other acute and chronic health conditions [8].

In July 2020, remdesivir received the marketing authorization from the European Medicines Agency [9], becoming the first drug indicated for the treatment of COVID-19. The pivotal study (ACTT-1) showed that remdesivir improves the time to recovery reducing the length of hospital stay in patients with COVID-19 and pneumonia, who require supplemental oxygen [10]. Remdesivir also showed a decrease in the disease progression by reducing the incidence of the need for new oxygen, high-flow oxygen, and mechanical ventilation. Also, non-mechanically ventilated patients had less progression or death versus placebo as showed in the post hoc analysis. Considering the dramatic situation occurred in Spain, the aim of our study was to estimate the impact that remdesivir would have had during the first wave of the COVID-19 pandemic.

Methods

This retrospective study estimated the resource savings for the SNHS and the deaths that would have been prevented if remdesivir had been available in Spain since the beginning of the first wave of the COVID-19 pandemic (from 31st January 2020 to 10th May 2020). Two scenarios were considered: a real-life scenario (without remdesivir), and an alternative scenario (with remdesivir) (Fig. 1).

Data resources

Epidemiology data and mortality rates were collected from the reports published by the Instituto de Salud Carlos III, under the Ministry of Health. Healthcare resource use was obtained from a literature review; international references were used whenever national data were not available. Databases consulted were Medline/Pubmed, Medes, and other official databases. All extracted data were validated by an expert group composed of four infectious disease specialists, an intensive care specialist, a medical microbiologist, and a hospital pharmacist.

Population

During the first wave, 233,328 patients with COVID-19 were diagnosed in Spain [11]. As reported by the Instituto de Salud Carlos III, 46.13% of them had to be hospitalized [11], while the prevalence of pneumonia was 83.84% [12]. Hence, it was estimated that 38.68% of all patients with COVID-19 had to be hospitalized due to pneumonia, and 7.45% were hospitalized because of other disorders [11, 12]. Of those hospitalized with pneumonia, it was estimated that 76.10% of patients required supplemental oxygen (Supplementary material, Fig. 1) [13].

According to the SNHS, the treatment with remdesivir in Spain is intended for hospitalized patients with COVID-19 and pneumonia who require low-flow oxygen therapy [14]. Therefore, we considered that 80.63% of those admitted in general wards who needed oxygen therapy, received low-flow oxygen. Besides, 10.70% and 6.61% of patients with and without pneumonia, respectively, were admitted in intensive care units (ICUs) (Supplementary material, Fig. 1) [12].

Resources use

This study considered the length of hospital stays and the number of hospitalized patients in general wards and ICUs during the first wave of the COVID-19 pandemic.

Patients were admitted in hospitals at a median of six days (interquartile range [IQR]: 3–9), from onset of symptoms [12]. The average hospital stay lasted an average of 10.40 days (range: 1–62) [15]. As ICUs admissions lasted an average of 23.00 days [16], it was estimated that admissions in general hospital wards lasted an average of 8.89 days. However, remdesivir reduces the recovery time in hospitalized patients with COVID-19 and supplemental oxygen, compared to placebo patients (rate ratio [RR]: 1.45; 95% confidence interval [CI]: 1.18–1.79) [10]. Therefore, it is estimated that remdesivir would have reduced the hospital stay in general wards up to 6.13 days (95% CI: 4.97–7.53) [10, 12, 15, 16].

In addition, remdesivir improves the clinical status of hospitalized patients with COVID-19 and pneumonia, who require supplemental oxygen. The probability of needing mechanical ventilation, high-flow oxygen devices, or extracorporeal membrane oxygenation (ECMO) at 15 days, was lower in patients treated with remdesivir compared to those in the placebo group (7.76% vs. 13.79%) [10]. A statistical testing was carried out, considering the null hypothesis (proportions are equal), and the alternative hypothesis (proportions are different). This analysis estimated that $p > 0.05$; therefore, the null hypothesis was rejected with a 5% level of statistical significance. Therefore, as patients who require mechanical ventilation, high-flow oxygen devices, or ECMO are assisted in the ICUs in Spain, we assumed that remdesivir would have reduced by 6.02% (95% CI: 5.19%–6.53%) the number of hospitalized patients in the ICUs (RR: 0.56; 95% CI: 0.49–0.61) (Supplementary material, Fig. 1).

Occupancy rates

The number of patients and the length of hospital stays allowed us to estimate the number of occupied beds in general hospital wards and ICUs. According to the Ministry of Health, there are 3,566 beds in ICUs and 112,219 beds in the public healthcare system [17]. Therefore, the occupancy rate was estimated in both scenarios over the whole capacity of the SNHS, in terms of total hospital beds and ICU beds.

Mortality

During the first wave of the pandemic, 11.90% of patients with COVID-19 died. The mortality rate in hospitalized patients on general wards was 20.61%, while for those in ICUs was 25.72% [12]. In hospitalized patients, the median time since the beginning of the symptoms until death was estimated in 11 days (IQR: 7–18) [12]; therefore, it was estimated that those patients had been in hospital for five days. Furthermore, as remdesivir reduced mortality by 70% (RR: 0.30; 95% CI: 0.14–0.64) in hospitalized patients with COVID-19 and supplemental oxygen [10], this new drug would have reduced the mortality rate up to 6.18% (95% CI: 2.89% – 13.19%) in general hospital wards (Fig. 1) [10, 12]. The mortality rate per age group and the number of patients necessary to treat (NNT) with remdesivir to prevent a COVID-19 death were also estimated.

Results

Population

The incidence of COVID-19 during the first wave, in the real-life setting, is shown in Fig. 2. Most of cases were registered between March and April, with a maximum of 10,140 patients on 25th March. Five days later, the peak number of hospitalized patients admitted to the general wards was recorded ($n = 4,209$). Besides, the maximum number of patients admitted in ICUs ($n = 469$) was recorded on 2nd and 3th April.

In the real-life scenario, of the 55,372 hospitalized patients with COVID-19 and pneumonia, receiving low-flow oxygen therapy, 5,919 patients were referred to the ICUs after 15 days, due to the worsening of the disease. However, in the alternative scenario, 3,332 patients (95% CI: 2,872–3,618) would have been referred to these units. Therefore, remdesivir would have avoided the admission of 2,587 patients (95% CI: 2,301–3,047) to the ICU, which implied a reduction of 43.71% (95% CI: 38.87% – 51.48%) in the number of hospitalized patients in the ICUs (Table 1).

Table 1
Hospitalized patients and deaths in both scenarios.

	Without remdesivir	With remdesivir	Difference
Hospitalized patients*			-
- On general wards after 15 days	49,453	52,040 (95% CI: 51,754–52,500)	2,587 (95% CI: 2,301– 3,047)
- ICUs after 15 days	5,919	3,332 (95% CI: 2,872– 3,618)	-2,587 (95% CI: -3,047 – [-2,301])
Deaths			
- On general wards	10,189	3,217 (95% CI: 1,515–6,826)	-6,972 (95% CI: -8,675 – [-3,364])
- ICUs	1,524	857 (95% CI: 739–930)	-667 (95% CI: -785 – [-594])
Deaths (other COVID-19 patients)**	16,053		NA
Total	27,767	20,128 (95% CI: 18,307–23,809)	-7,639 (95% CI: -9,460 – [-3,958])

Notes: *Hospitalized patients with COVID-19 and pneumonia requiring low-flow oxygen therapy at the time of hospitalization. It is the target population for the treatment with remdesivir. **Non-hospitalized patients, hospitalized patients with pneumonia who did not require low-flow oxygen and hospitalized patients with other disorders, different to pneumonia. Abbreviations: NA: not aplicable. Sources: Instituto de Salud Carlos III. Informe no 33, 2020.[12]

Occupied beds

The maximum occupancy of beds earmarked for COVID-19 patients, in general hospital wards, was registered on 5th April, with 32,264 occupied beds. However, remdesivir reduces the length of the hospital stay, it is estimated that 5,656 hospital beds (95% CI: 1,283–7,880) would have been made available for other patients on that date. The number of available beds would have increased by 17.53% (95% CI: 3.98% – 24.42%) at the time of the highest occupancy rate. The green area (Fig. 3) shows the number of beds that would have been released per day, if remdesivir had been available since the beginning of the first wave.

Regarding the ICUs, the highest occupancy records were registered on 17th April, with 7,088 occupied beds. As remdesivir improves the clinical status of patients with COVID-19 and pneumonia who require low-flow oxygen therapy, this new drug would have made available 1,700 beds (95% CI: 1,512–2,000) for other patients on that date. Therefore, the number of available beds would have increased by 23.98% (95% CI: 21.33% – 28.22%) during the peak of occupancy rate of ICUs (Fig. 4).

Mortality

During the first wave, 10,189 patients and 1,524 patients died in general hospital wards and ICUs, respectively. However, as remdesivir reduces the mortality rate in hospitalized patients with COVID-19 and pneumonia receiving low-flow oxygen therapy, this new drug would have avoided 6,972 deaths (95% CI: 3,364–8,675) in general wards. Furthermore, as remdesivir avoided at least half of the ICU admissions, 667 deaths (95% CI: 594–785) would have been avoided in these wards (Table 1).

According to our results, the overall mortality rates in hospitalized patients with COVID-19 and pneumonia who require low-flow oxygen therapy are 7.36% (95% CI: 4.07% – 14.01%) and 21.15%, in the scenarios with and without remdesivir, respectively, with an absolute risk reduction of death of 13.80% (95% CI: 7.15% – 17.08%). Therefore, it is necessary to treat seven hospitalized patients (95% CI: 6–14) with COVID-19 and pneumonia, who require low-flow oxygen therapy, with remdesivir, to prevent a death.

We estimated that other 16,053 patients with COVID-19 died in the first wave (i.e. non-hospitalized patients, hospitalized patients with pneumonia who did not require low-flow oxygen and hospitalized patients with other disorders, different to pneumonia). Therefore, in the remdesivir scenario, deaths would have amounted to 20,128 (95% CI: 18,307–23,809), avoiding 7,639 deaths (95% CI: 3,958–9,460), which implies a 27.51% reduction (95% CI: 14.25% – 34.07%) in the mortality rate due to COVID-19 (Tables 1 and 2).

Table 2 shows that mortality rates increased by age. As can be seen, deaths amounted to 6,619 and 17,371 in patients between 70–79 and over 80 years, respectively, in the real-life scenario. However, remdesivir would have prevented 1,821 deaths (95% CI: 943–2,255) and 4,779 deaths (95% CI: 2,476–5,918) in both groups, respectively.

Table 2
Total deaths (general wards and ICUs) by group age.

Age (years)	Without remdesivir	With remdesivir			Difference		
		Average	95% CI (inferior)	95% CI (superior)	Average	95% CI (inferior)	95% CI (superior)
<2	3	2	2	2	1	0	1
2–4	0	0	0	0	0	0	0
5–14	1	1	1	1	0	0	0
15–29	38	27	25	32	10	5	13
30–39	85	62	56	73	23	12	29
40–49	294	213	194	252	81	42	100
50–59	891	646	587	764	245	127	303
60–69	2,466	1,788	1,626	2,115	678	351	840
70–79	6,619	4,798	4,364	5,675	1,821	943	2,255
≥ 80	17,371	12,592	11,453	14,895	4,779	2,476	5,918
Total	27,767	20,128	18,307	23,809	7,639	3,958	9,460

Abbreviations: CI: confidence interval.

Discussion

The COVID-19 pandemic has implied a significant burden for healthcare systems. The rising number of cases has increased the resource use, leading to drug shortages and an insufficient number of beds in hospitals [4]. To expand the capacity of the SNHS, some temporary field hospitals were opened, such as the pavilions of the city fair in Madrid [3]. Furthermore, due to the lack of resources, only patients with pneumonia who were in serious condition were hospitalized during the peak of the pandemic. Most COVID-19 patients were sent to nearby converted hotels or their homes to be treated by general practitioners [4, 18].

Our results showed that the maximum number of hospitalized patients with this infection was reached on 5th April, when 32,264 beds were occupied in general hospital wards, while 7,088 ICU beds were occupied on 17th April. In line with our research, the Institute for Health Metrics and Evaluation (IHME) estimated that the maximum number of occupied beds in general wards was 46,081 on 31st March, and 6,430 beds in ICUs on 4th April. However, both studies differ in their methodology, as we estimated the healthcare resource use according to official records and observational studies carried out in Spain, while the IHME developed a microsimulation model based on death reports [19].

According to our research, the capacity of the ICUs almost doubled during the first wave, as the bed occupancy rate reached 198.77%. This dramatic situation prompted the development of a contingency plan by the Spanish Society of Critical, Intensive and Coronary Medicine Units (SEMICYUC) and other intensive medicine organizations. The new programme was based on increasing the number of ICU beds and other healthcare resources, to avoid the collapse of the SNHS in the following waves and future pandemics [20]. In consonance with these recommendations, Lacasa and colleagues estimated an algorithm to provide optimal rerouting strategies to ICU patients. Their approach was validated using real-life data from Spain; they concluded that 600 beds could have been available if using local sharing and over 1,300 beds with countrywide sharing. This strategy would improve the management of COVID-19, particularly for patients who would not otherwise have access to ICUs. However, their approach had some limitations, as they considered the transportation of unstable patients in mobile ICUs, and an unlimited number of ambulances and human resources [21]. Besides, the mortality rate in hospitalized patients on general wards was 20.61% [12], which is in line with a previous study, that reported a mortality rate of 21.1% in hospitalized patients with COVID-19 [15].

The efficacy of remdesivir in the management of COVID-19 was demonstrated in several studies [9]. Olender and colleagues analysed its efficacy in a non-randomized cohort study, using a propensity score model, and an inverse probability of treatment weighting method. The participants were hospitalized patients with COVID-19, pulmonary infiltrates, and either had oxygen saturation of $\leq 94\%$ on room air or were receiving supplemental oxygen. Their results showed that 74.40% of patients in the remdesivir group versus 59.00% in the standard of care group achieved the primary recovery endpoint at day 14 (adjusted odds ratio: 2.03 [95% CI: 1.34–3.08], $p < 0.001$). They also observed a 62% lower adjusted odds of all-cause death [22]. In addition, the double-blind, randomized, and placebo-controlled ACTT-1 trial showed that remdesivir improves the time to recovery and clinical status of hospitalized patients with COVID-19 and pneumonia, who require supplemental oxygen [10], resulting in a reduction in the length of hospital stays and the number of ICU admissions. Despite the ACTT-1 trial did not reach a statistically significant difference in mortality in the overall study population, a post hoc analysis showed that remdesivir significantly reduced the mortality in hospitalized patients with COVID-19 and supplemental oxygen.

Our results showed that remdesivir would have made available up to 7,880 beds in general wards and 2,000 ICU beds for other patients at the peak of the occupancy rates, respectively. Therefore, this new drug would have relieved the pressure on hospitals and the SNHS, due to the pandemic. Furthermore, remdesivir would have implied a 27.51% reduction (95% CI: 14.25% – 34.07%) in deaths due to COVID-19 during the first wave in Spain. It should be noted that a multi-country, open-label randomized trial developed by the WHO showed that remdesivir was not effective in reducing the mortality rate in hospitalized patients with COVID-19 (RR = 0.95 [95% CI: 0.81–1.11], $p = 0.50$) [23]. Although this conclusion differs from previous evidence, it should be noted that our results refer to those patients who require low-flow oxygen therapy (a National Early Warning Score [NEWS] of 5) [24], according to the pharmacological protocol used in the SNHS [14]. In addition, the SOLIDARITY trial compared the efficacy of remdesivir in patients with or without mechanical ventilation, regardless of the oxygen delivery system (e.g. low-flow or high-flow devices) [23].

Our study has some limitations that need to be addressed. First, due to the lack of information about the clinical status of COVID-19 patients, we assumed that 76.1% of hospitalized patients with pneumonia required supplemental oxygen, according to the US records [13]. Nevertheless, a group of experts agreed that this percentage was similar to the clinical practice in Spain. Second, we considered that hospitalized patients who require mechanical ventilation, high-flow oxygen devices, or ECMO are assisted in the ICUs in Spain. Although this practice is widely spread, the management of COVID-19 patients may differ in some Spanish regions. Third, since there are no real-life studies about the efficacy of remdesivir in our country, we assumed the results of the ACTT-1 trial. Fourth, although we considered official sources, our results may be biased due to notification delays and the overwhelmed healthcare system. Fifth, given that the reduction of mortality rates by age group in patients receiving remdesivir was not estimated in the ACTT-1 trial, we estimated the number of prevented deaths by age group using the reduction in the mortality rate for the whole population of the trial. Sixth, since the potential impact on mortality due to the controversial use of other drugs, such as IL6 inhibitors, is unknown, it has not been considered in our study.

Despite of these limitations, the main contributions of our study are: 1) the assessment of the healthcare resources used during the first wave of the pandemic (in terms of occupied beds in general wards and ICUs) in Spain and 2) the potential number of beds available in general wards and ICUs, if remdesivir would have been used for the treatment of COVID-19. Our results showed that this new drug would have avoided almost half of the ICU admissions, so it would have reduced the pressure on the public system, providing a more efficient use of resources. Consequently, in the following waves of the pandemic, although the preventive measurements have reduced the burden of COVID-19 for the SNHS, as well as the death toll [25], remdesivir will reduce even more the use of healthcare resources, while avoiding preventable deaths.

Conclusions

The treatment with remdesivir in hospitalized patients with COVID-19 and pneumonia, who require low-flow oxygen therapy, would have reduced by 17.53% and 23.98% the number of occupied beds in hospitals and ICUs, respectively. Therefore, it would have lessened the pressure of the SNHS during the first wave, providing a better strategy for the management of COVID-19 in our country. Furthermore, remdesivir would have prevented 27.51% of deaths due to this infection. Therefore, in the following waves, this new drug will be able to provide a more efficient use of resources, while reducing the burden of COVID-19 for society.

List Of Abbreviations

SNHS: Spanish National Health System

SARS-Cov-2: Severe acute respiratory syndrome coronavirus 2

COVID-19: Coronavirus disease 2019

WHO: World Health Organisation

ICUs: Intensive care units

ECMO: Extracorporeal membrane oxygenation

NNT: Number necessary to treat

IHME: Institute for Health Metrics and Evaluation

SEMICYUC: Spanish Society of Critical, Intensive and Coronary Medicine Units

NEWS: National Early Warning Score

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The study data can be found in the following reference list

Competing interests

AS reports grants and personal fees from Pfizer and Gilead Sciences, and personal fees from Merck, Shionogi, and Menarini, outside the submitted work. RM reports honorarium from Gilead Sciences, during the conduct of the study, and personal fees from Gilead Sciences, ViiV, Merck Sharp and Dohme, and Janssen Cilag, outside the submitted work. SG reports personal fees from Gilead Sciences, during the conduct of the study; personal fees from Gilead Sciences, Pfizer, and MSD, outside the submitted work. RGF reports grants and honorarium for research from Gilead Sciences and honorarium for consulting from ViiV, outside the submitted work. AC is a Gilead Sciences employee. AGD and IPR work at Weber, company that received fees from Gilead Sciences, during the conduct of the study. AHV, JCF, and JSM have nothing to disclose.

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Authors' contributions

AC and AGD participated in the conception and design of the study. AS, RM, JSM, SG, RG, IPR, and AGD participated in the acquisition of data. ACG, IPR, AHV and AGD participated in the analysis and interpretation of data. IPR wrote the draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version to be published.

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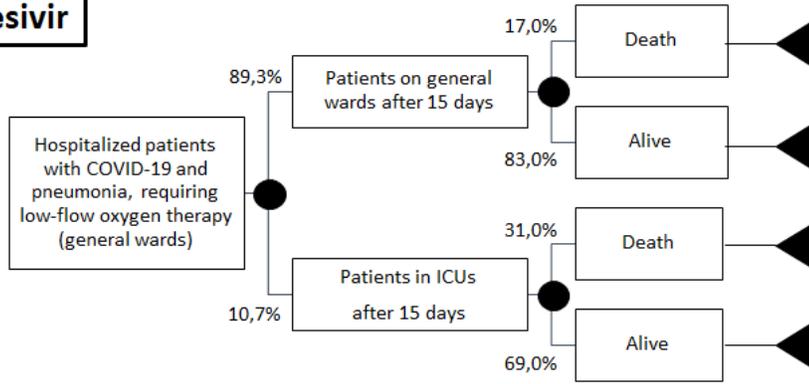
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Figures

Without remdesivir



With remdesivir

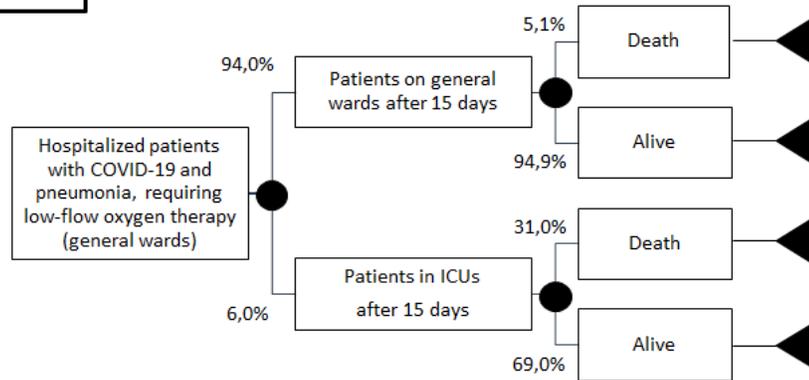


Figure 1

Scheme of the decision model. Abbreviations: ICUs: intensive care units.

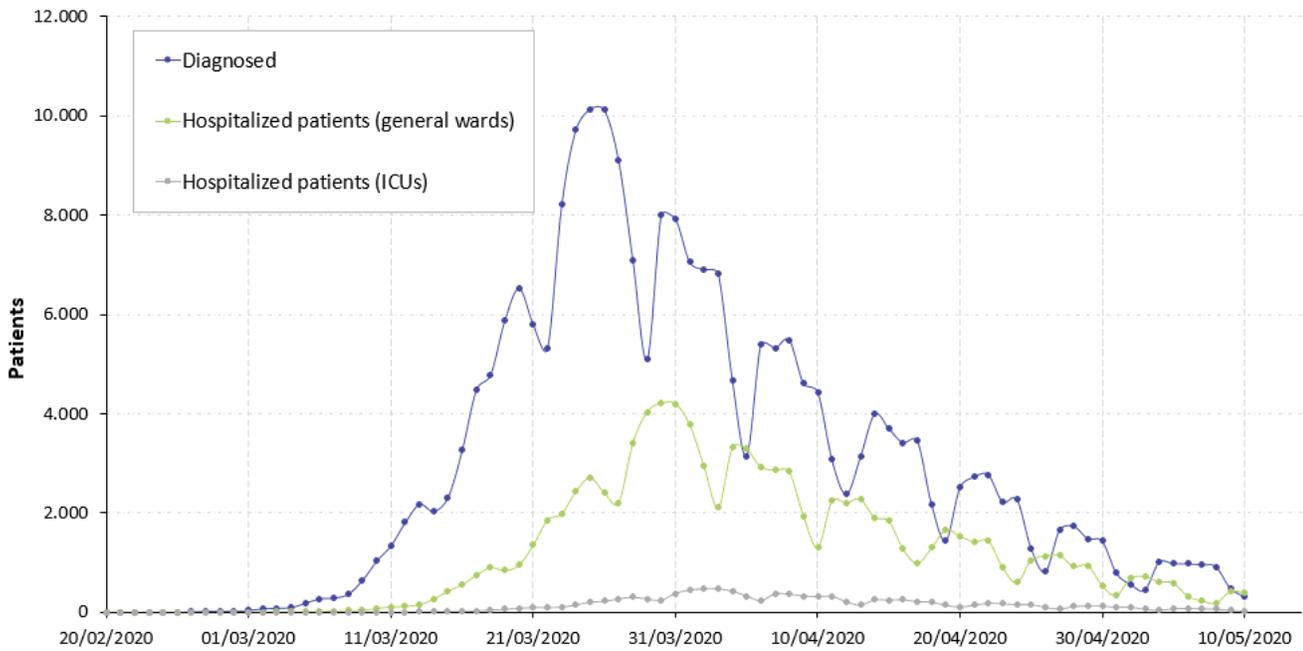


Figure 2

Incident COVID-19 patients during the first wave in Spain. Abbreviations: ICUs: intensive care units.

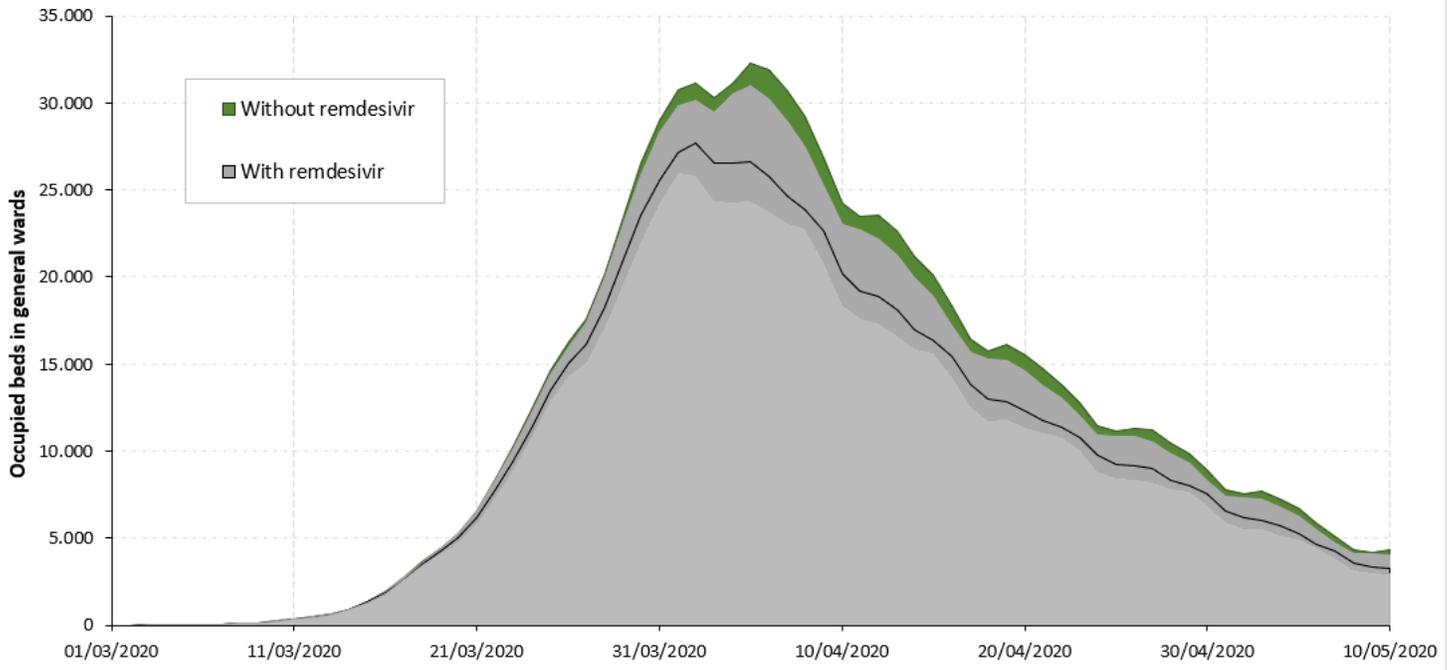


Figure 3

Occupied beds in general wards in both scenarios.

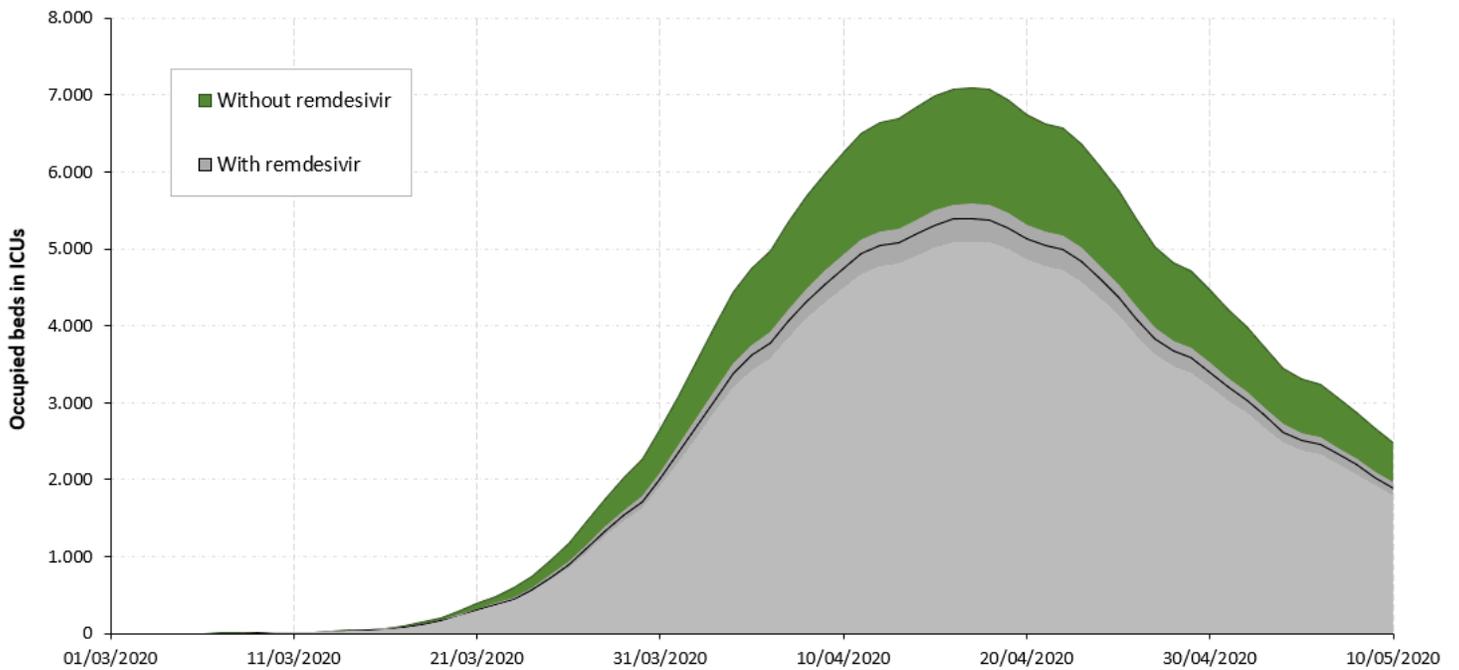


Figure 4

Occupied beds in ICUs in both scenarios. Abbreviations: ICUs: intensive care units.

Supplementary Files

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